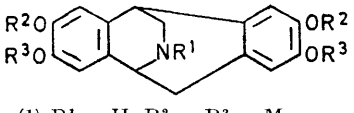
# Studies on the Syntheses of Heterocyclic Compounds. Part DXXVI.[1] A Novel Synthesis of Isopavine-type Alkaloids. Total Synthesis of (±)-Reframidine

By **Tetsuji Kametani,* Shoji Hirata,** and **Kunio Ogasawara,** Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan

A new synthetic method for isopavine derivatives, through one-step ring opening and ring closure of an aziridinium intermediate, and its application to a total synthesis of (±)-reframidine (3), are described.

BATTERSBY and YEOWELL [2] reported the synthesis of the isopavine system (1) before the discovery of naturally occurring isopavine alkaloids.[3] Later syntheses [4-8] were




(1) $R^1$ = H, $R^2$ = $R^3$ = Me
(2) $R^1$ = $CH_2Ph$, $R^2R^3$ = $CH_2$
(3) $R^1$ = Me, $R^2R^3$ = $CH_2$

all based on this original method. We have now developed a new type of isopavine synthesis involving a one-step ring opening and ring closure, which has been successfully applied to a total synthesis of (±)-reframidine (3).[7]

As the key reaction for the construction of the isopavine framework, we employed the intermolecular diazomethane–iminium insertion followed by ring expansion originally reported by Leonard and his co-workers.[9] Pfeifer and his co-workers [10] observed that this reaction could be applied to hydrastinine (4) and cotarnine (5) to give the ring-expanded azepine derivatives (11) and (12), respectively. Recently Bernhard and Snieckus [11] showed that the aziridinium perchlorate (8) was an intermediate in the reaction with hydrastinine perchlorate (8).

[1] Part DXXV, T. Kametani, E. Taguchi, K. Yamaki, A. Kozuka, and T. Terui, *Chem. and Pharm. Bull.* (*Japan*), 1973, **21**, 1124; part of the present work was reported as a preliminary communication in *Chem. and Pharm. Bull* (*Japan*), 1973, **21**, 893.

[2] A. R. Battersby and D. A. Yeowell, *J. Chem. Soc.*, 1958, 1988.

[3] *Cf.* T. Kametani, 'The Chemistry of the Isoquinoline Alkaloids,' Hirokawa, Tokyo, and Elsevier, Amsterdam, 1968, p. 235.

[4] S. M. Kupchan and A. Yoshitake, *J. Org. Chem.*, 1969, **34**, 1062.

[5] M. Sainsbury, D. W. Brown, S. F. Dyke, and G. Hardy, *Tetrahedron*, 1969, **25**, 1881.

[6] D. W. Brown, S. F. Dyke, G. Hardy, and M. Sainsbury, *Tetrahedron Letters*, 1969, 1515.

[7] S. F. Dyke and A. C. Ellis, *Tetrahedron*, 1971, **27**, 3803.

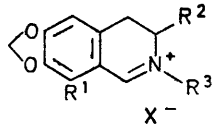
[8] S. F. Dyke and A. C. Ellis, *Tetrahedron*, 1972, **28**, 3999.

[9] (*a*) N. J. Leonard and K. Jann, *J. Amer. Chem. Soc.*, 1962, **84**, 4806; (*b*) *Cf.* D. R. Crist and N. J. Leonard, *Angew. Chem. Internat. Edn.*, 1968, **8**, 962.

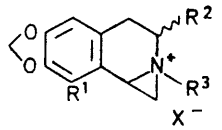
[10] B. Goeber, S. Pfeifer, V. Hanuš, and G. Engelhardt, *Arch. Pharm.*, 1968, **301**, 763.

[11] H. O. Bernhard and V. Snieckus, *Tetrahedron*, 1971, **27**, 2091.

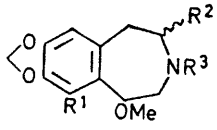
We were interested in effecting a similar reaction with a 3-(alkoxyphenyl)isoquinolinium iodide (6) to afford an aziridinium iodide (9), which might then be transformed into an isopavine (2) *via* one-step ring expansion and ring-closure involving intramolecular attack by the electron-rich alkoxyphenyl group.



(4) $R^1 = R^2 = H$, $R^3 = Me$, $X = ClO_4$
(5) $R^1 = OMe$, $R^2 = H$, $R^3 = Me$, $X = ClO_4$
(6) $R^1 = H$, $R^2 = Mdop$, $R^3 = CH_2Ph$, $X = I$
(7) $R^1 = H$, $R^2 = Mdop$, $R^3 = Me$, $X = I$



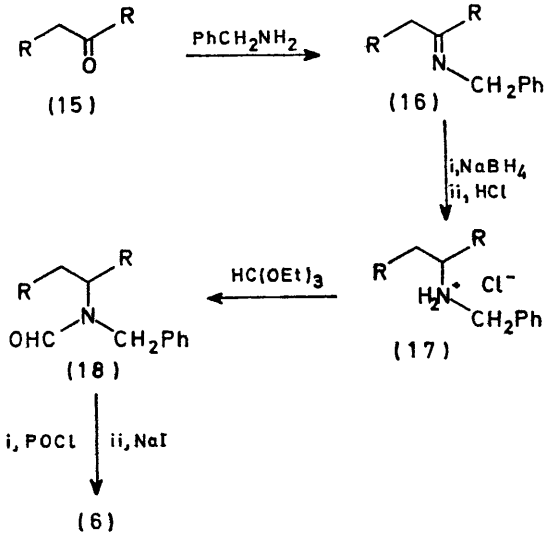
(8) $R^1 = R^2 = H$, $R^3 = Me$, $X = ClO_4$
(9) $R^1 = H$, $R^2 = Mdop$, $R^3 = CH_2Ph$, $X = I$
(10) $R^1 = H$, $R^2 = Mdop$, $R^3 = Me$, $X = I$



(11) $R^1 = R^2 = H$, $R^3 = Me$
(12) $R^1 = OMe$, $R^2 = H$, $R^3 = Me$
(13) $R^1 = H$, $R^2 = Mdop$, $R^3 = CH_2Ph$
(14) $R^1 = H$, $R^2 = Mdop$, $R^3 = Me$

Mdop = 3,4-Methylenedioxyphenyl

The 3-substituted isoquinolinium iodide (6), prepared as shown in Scheme 1, was treated with an excess of ethereal diazomethane at 0° in methylene chloride. The amorphous product, possibly the crude aziridinium iodide (9), was treated with methanolic hydrochloric acid for 5 days at room temperature to afford the isopavine (2) in 4·2% yield in addition to the ring expanded 3-benzazepine (13) (28·0%). The identification of the isopavine (2) was confirmed by microanalysis and spectral data, especially its mass spectrum, which showed fragmentation patterns typical of isopavine alkaloids.[12,13]

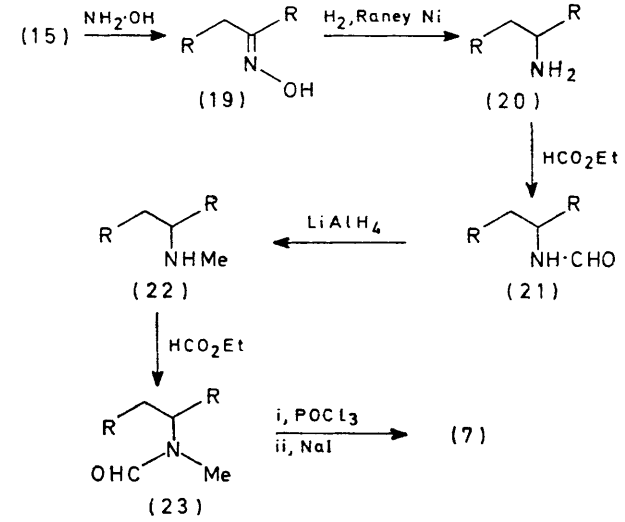



R = 3,4-Methylenedioxyphenyl

SCHEME 1

The 3-benzazepine (13) was exclusively formed, in 49·0% yield, from the crude aziridinium iodide (9) by boiling with methanolic 3% hydrogen chloride; the product gave the isopavine (2) in 69·9% yield on treatment with ethanolic hydrochloric acid (1 : 1) at room temperature for 5 days.

The foregoing sequence was then applied to the synthesis of reframidine (3). The key isoquinolinium iodide (7), prepared as shown in Scheme 2, was treated with an excess of ethereal diazomethane. A solution of the resulting crude aziridinium iodide (10) in 6N-hydrochloric acid was kept at room temperature for 1




R = 3,4-Methylenedioxyphenyl

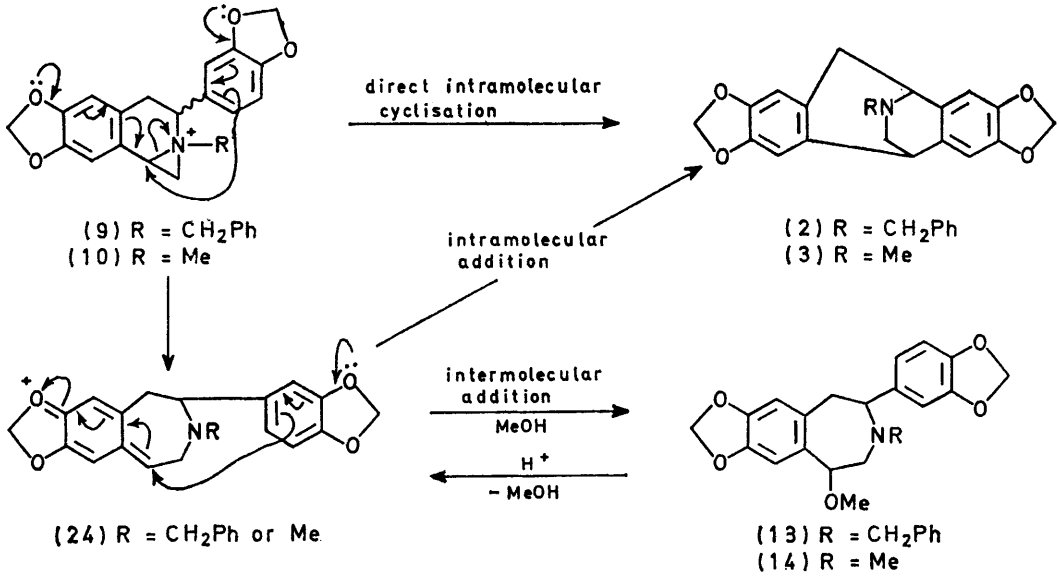
SCHEME 2

[12] L. Dolejš and V. Hanuš, *Coll. Czech. Chem. Comm.*, 1968, **33**, 600.

[13] L. Dolejš and J. Slavík, *Coll. Czech. Chem. Comm.*, 1968, **33**, 3917.

week to afford (±)-reframidine (3) in 20% yield. Reframidine (3) was also formed in 35% yield when the 3-benzazepine (14), obtained in 20% yield by refluxing the crude aziridinium iodide (10) with methanolic 1% hydrogen chloride, was treated with 6N-hydrochloric acid at room temperature for 1 week. The (±)-reframidine (3) was identified by comparison of i.r., n.m.r., and mass spectra with data supplied by Professor S. F. Dyke.

Although there was no evidence for the formation of the azepines (13) and (14), the ready conversion into the isopavines (2) and (3) suggests that the aziridinium ring was not attacked intramolecularly by the 3-(alkoxyphenyl) group, but that the 6-oxygen atom on the isoquinoline ring was involved in forming a transient quinonoid intermediate (24), which was then attacked either intramolecularly by the 3-(alkoxyphenyl) group or intermolecularly by a methoxy-group, depending on the reaction conditions (Scheme 3).




SCHEME 3

This novel method should be applicable to the synthesis of other naturally occurring isopavine alkaloids.

## EXPERIMENTAL

N.m.r. spectra were measured with a Hitachi H-60 spectrometer (solutions in deuteriochloroform; tetramethylsilane as internal reference). I.r. spectra were taken with a type EPI-3 Hitachi recording spectrometer and a Hitachi-215 grating spectrometer, and mass spectra with a Hitachi RMU-7 spectrometer.

*N-Benzyl-1,2-bis-(3,4-methylenedioxyphenyl)ethylamine-* (17).—A mixture of 3,4:3′,4′-bis(methylenedioxy)deoxybenzoin (15) (9·54 g) and benzylamine (3·6 g) was heated at 150° for 24 h, cooled, and dissolved in chloroform–methanol (1 : 1; 100 ml), to which sodium borohydride (4 g) was added in portions at room temperature. After 3 h the solvent was evaporated off; the residue was decomposed with water and extracted with ether. The extract was washed with water, dried ($K_2CO_3$), and evaporated. The residue was treated with 35% hydrochloric acid and the precipitate was filtered off, washed with ether, made basic with 28% ammonia, and then extracted with ether. The extract was washed with water, dried ($K_2CO_3$), and evaporated to afford the amine (17) (8·4 g) as *granules*, m.p. 75—78° (from n-hexane) (Found: C, 73·55; H, 5·9. $C_{23}H_{21}NO_4$ requires C, 73·6; H, 5·65%), $\nu_{max.}$ (Nujol) 3400—3300 $cm^{-1}$ (NH), *m/e* 375 ($M^+$). The hydrochloride formed *prisms*, m.p. 240—240·5° (from aqueous ethanol) (Found: C, 67·4; H, 5·45; N, 3·4. $C_{23}H_{22}ClNO_4$ requires C, 67·05; H, 5·85; N, 3·4%).

*N-Benzyl-N-[1,2-bis-(3,4-methylenedioxyphenyl)ethyl]-formamide* (18).—A mixture of the hydrochloride of (17) (6·5 g) and triethyl orthoformate [14] (5 g) was heated at 100° for 15 h. After removal of low-boiling material under reduced pressure, the mixture was chromatographed on silica gel (100 g) to give the *formamide* (18) (5·0 g) as a pale yellow syrup (Found: C, 71·55; H, 5·5; N, 3·45. $C_{24}H_{21}NO_5$ requires C, 71·45; H, 5·25; N, 3·45%), $\nu_{max.}$ (film) 1650 $cm^{-1}$ (CO), τ($CDCl_3$) 7·04—5·30 (5H, m, 2 × $CH_2$ and CH), 4·20 and 4·16 (4H, each s, 2 × O·$CH_2$·O), 3·70—2·70 (10H, m, ArH), and 1·83 and 1·74 [1H, each s (1 : 3), CHO, tautomeric forms], *m/e* 403 ($M^+$) and 268 ($M^+$ —135).

*2-Benzyl-3,4-dihydro-6,7-methylenedioxy-3-(3,4-methylenedioxyphenyl)isoquinolinium Iodide* (6).—A mixture of the amide (18) (4·17 g), phosphoryl chloride (4·0 g), and dry benzene (200 ml) was refluxed for 2 h, then cooled. An oily substance which separated was washed with n-hexane and dissolved in hot water, to which potassium iodide (5 g) was added to afford yellow crystals. Recrystallisation from ethanol gave the salt (6) (4·5 g) as *granules*, m.p. 209·5—210·0° (decomp.) (Found: C, 56·3; H, 4·2. $C_{24}H_{20}INO_4$ requires C, 56·2; H, 3·95%), $\nu_{max.}$ (Nujol) 1635 $cm^{-1}$ ($>C{=}\overset{+}{N}$), τ[$CDCl_3$–$(CD_3)_2SO$] 6·80—6·05 (2H, m,

[14] T. Kametani, K. Ogasawara, and T. Harada, *J. Pharm. Soc. Japan*, 1968, **88**, 163.

$CH_2$), 5·26—4·42 (1H, m, CH), 4·08 and 3·87 (4H, each s, 2 × O·$CH_2$·O), 3·35—2·45 (10H, m, ArH), and 0·01 (1H, s, 1-H), *m/e* 386 ($M^+$ −127).

3-*Benzyl*-2,3,4,5-*tetrahydro*-1-*methoxy*-7,8-*methylenedioxy*-4-(3,4-*methylenedioxyphenyl*)-1H-3-*benzazepine* (13).—To a solution of the isoquinolinium iodide (6) (1·5 g) in methylene chloride (60 ml), an excess of ethereal diazomethane was added at −10°. Next day the solvent was removed to leave a brown solid, which was dissolved in methanolic 3% hydrogen chloride (30 ml) and refluxed overnight. The solvent was removed and the residue was extracted with methylene chloride; the extract was washed with 10% ammonia and water, dried ($K_2CO_3$), and evaporated. The product was chromatographed to give the benzazepine (13) (0·6 g) as *needles*, m.p. 141—142° (Found: C, 72·7; H, 6·15; N, 3·05. $C_{26}H_{25}NO_5$ requires C, 72·35; H, 5·85; N, 3·25%), τ($CDCl_3$) 7·81—6·16 (7H, m, 3 × $CH_2$ and CH) 6·77 (3H, s, O·$CH_3$), 4·13 (4H, s, 2 × O·$CH_2$·O), 3·65 (1H, s, ArH), 3·31 (2H, s, ArH), 3·28 (1H, s, ArH), 3·19 (1H, s, ArH), and 2·80 (5H, s, ArH), *m/e* 431 ($M^+$). The hydrochloride formed *prisms*, m.p. 194—194·5° (decomp.) (from ethanol) (Found: C, 67·05; H, 5·8; N, 2·95. $C_{26}H_{26}ClNO_5$ requires C, 66·7; H, 5·6; N, 3·0%).

N-*Benzyl*-N-*nor-reframidine* (2).—(*a*) A solution of compound (13) (100 mg) in ethanol and 35% hydrochloric acid (3 : 5; 8 ml) was set aside at room temperature for 5 days, then basified with 28% ammonia and extracted with methylene chloride. The extract was washed with water, dried ($K_2CO_3$), and evaporated to give a pale brown syrup (90 mg), which was chromatographed on silica gel (3 g) to afford a pale yellow powder (2) (65 mg) identical with the sample prepared in (*b*).

(*b*) To a solution of the isoquinolinium iodide (6) (5·3 g) in methylene chloride (150 ml), excess of ethereal diazomethane was added at −5°. Next day the solvent was evaporated off and a solution of the residue in methanol (20 ml) was added to 6N-hydrochloric acid (100 ml) with stirring. The mixture was kept at room temperature for 4 days, then made basic with 28% ammonia, and extracted with methylene chloride. The extract was washed with water and dried ($K_2CO_3$). Removal of methylene chloride left a pale brown oil (4·8 g), which was chromatographed on silica gel (150 g) to afford a pale yellow powder (2) (300 mg) in addition to compound (13) (1·3 g). N-*Benzyl*-N-*nor-reframidine* (2) crystallised from ethanol to give a powder, m.p. 86—88° (Found: C, 75·4; H, 5·15. $C_{25}H_{21}NO_4$ requires C, 75·15; H, 5·3%), τ($CDCl_3$) 7·40—6·10 (6H, m, 2 × $CH_2$ and 2 × CH), 4·23—4·10 (4H, m, 2 × O·$CH_2$·O), 3·54, 3·42, 3·39, and 3·32 (4H, each s, ArH), and 2·70 (5H, s, ArH), *m/e* 399 ($M^+$), 308 ($M^+$ −91), 280 ($M^+$ −119), and 264 ($M^+$ −135).

3,4:3′,4′-*Bis*(*methylenedioxy*)*deoxybenzoin Oxime* (19).—A mixture of the ketone (15) (15 g), hydroxylamine hydrochloride (5·6 g), sodium hydroxide (3·1 g), and ethanol (500 ml) was refluxed for 3 h. Ethanol (300 ml) was evaporated off, and the precipitate was removed and recrystallised from ethanol to give the oxime (19) (16 g) as *needles*, m.p. 159—160° (Found: C, 64·1; H, 4·4; N, 4·4. $C_{16}H_{13}NO_5$ requires C, 64·2; H, 4·4; N, 4·7%), $\nu_{max.}$ ($CHCl_3$) 3480 $cm^{-1}$ (OH).

1,2-*Bis*-(3,4-*methylenedioxyphenyl*)*ethylamine* (20).—A solution of the oxime (19) (12 g) in tetrahydrofuran (300 ml) was hydrogenated over Raney nickel at 45 kg $cm^{-2}$ to afford the amine (20) (12 g); the hydrochloride crystallised from methanol to afford *needles*, m.p. 261—262° (Found: C, 59·35; H, 5·15; N, 4·35. $C_{16}H_{16}ClNO_4$ requires C, 59·7; H, 5·0; N, 4·35%).

N-[1,2-*Bis*-(3,4-*methylenedioxyphenyl*)*ethyl*]*formamide* (21).—A mixture of the amine (20) (12 g) and ethyl formate (100 ml) was refluxed for 1·5 h. Evaporation of ethyl formate left a solid, which crystallised from benzene to give the amide (21) (12 g) as *needles*, m.p. 162—163° (Found: C, 65·1; H, 4·7; N, 4·4. $C_{17}H_{15}NO_5$ requires C, 65·15; H, 4·8; N, 4·45%), $\nu_{max.}$ (KBr) 3350 (NH) and 1660 $cm^{-1}$ (CO), τ($CDCl_3$) 7·01 (2H, d, *J* 7 Hz, $CH_2$), 4·81 (1H, m, CH), 2·66 (1H, d, *J* 6 Hz, NH), and 1·89 (1H, s, CHO).

N-*Methyl*-1,2-*bis*-(3,4-*methylenedioxyphenyl*)*ethylamine* (22).—To a stirred suspension of lithium aluminium hydride (4·4 g) in dry tetrahydrofuran (100 ml), a solution of the amide (21) (10 g) in dry tetrahydrofuran (100 ml) was added dropwise. Stirring was continued for 3 h under reflux, and the excess of lithium aluminium hydride was then decomposed with 10% sodium hydroxide solution. The inorganic precipitate was filtered off and the solvent was removed to leave a solid (22) (7·0 g), τ($CDCl_3$) 7·82 (3H, s, N·$CH_3$), whose hydrochloride yielded *needles*, m.p. 239—240° (from methanol) (Found: C, 60·5; H, 5·2; N, 4·25. $C_{17}H_{18}ClNO_4$ requires C, 60·8; H, 5·4; N, 4·15%).

N-*Methyl*-N-[1,2-*bis*-(3,4-*methylenedioxyphenyl*)*ethyl*]-*formamide* (23).—A mixture of the amine (22) (7·0 g) and ethyl formate (200 ml) was refluxed for 7 h. Evaporation of ethyl formate left a viscous syrup (6·8 g), which was chromatographed on silica gel (150 g) to give a *syrup* (Found: C, 66·3; H, 5·25; N, 4·35. $C_{18}H_{17}NO_5$ requires C, 66·05; H, 5·25; N, 4·3%), $\nu_{max.}$ ($CHCl_3$) 1660 $cm^{-1}$ (CO), τ($CDCl_3$), 7·38 (3H, s, N·$CH_3$), 6·88 (2H, d, *J* 7 Hz, $CH_2$), 5·36 (1H, t, CH), 4·07 and 4·02 (4H, each s, 2 × O·$CH_2$·O), 3·43—3·15 (6H, m, ArH), and 2·08 (1H, s, CHO).

3,4-*Dihydro*-2-*methyl*-6,7-*methylenedioxy*-3-(3,4-*methylenedioxyphenyl*)*isoquinolinium Iodide* (7).—A mixture of the amide (23) (3·2 g), phosphoryl chloride (3·2 g), and dry benzene (200 ml) was refluxed for 3 h. The solvent was evaporated off to leave a brown solid, which was dissolved in methanol (200 ml) containing sodium iodide (5·0 g). Evaporation of methanol left a yellowish solid, which was taken up with chloroform. Evaporation of the extract left compound (7) (2·7 g) as yellow *prisms*, m.p. 233—234° (from methanol) (Found: C, 49·45; H, 3·8; N, 3·2. $C_{18}H_{16}INO_4$ requires C, 49·45; H, 3·7; N, 3·2%), $\nu_{max.}$ (KBr) 1660 $cm^{-1}$ ($>C=\overset{+}{N}$), τ($CDCl_3$) 2·41 (1H, s, 8-H), and 0·07 (1H, s, 1-H).

2,3,4,5-*Tetrahydro*-1-*methoxy*-3-*methyl*-7,8-*methylenedioxy*-4-(3,4-*methylenedioxyphenyl*)-1H-3-*benzazepine* (14).—To a solution of isoquinolinium iodide (7) (2·0 g) in methylene chloride (300 ml), an excess of ethereal diazomethane was added at 0°. Next day the solvent was removed to leave a brown solid, which was dissolved in methanolic 1% hydrogen chloride. The solution was refluxed for 5 h, the solvent was evaporated off, and the residue was extracted with chloroform. The extract was washed with 10% ammonia and water, dried ($Na_2SO_4$), and evaporated. The resulting viscous syrup was chromatographed on silica gel (60 g). Elution with chloroform afforded compound (14) (400 mg) as a reddish syrup, τ($CDCl_3$) 7·92 (3H, s, N·$CH_3$), 6·52 (3H, s, O·$CH_3$), 5·43 (1H, dd, *J* 9 and 3 Hz, *CH*·O·$CH_3$), and 7·55—7·03 (5H, m, ArH), *m/e* 355 ($M^+$). A mixture of compound (14) (30 mg) and methyl iodide (2 ml) was kept overnight and then evaporated to

afford the *methiodide* (40 mg) as a pale yellow powder (from ether), m.p. 189—190° (Found: N, 2·95. $C_{21}H_{24}INO_5$ requires N, 2·8%).

(±)-*Reframidine* (3).—(*a*) A solution of compound (14) (270 mg) in 6N-hydrochloric acid was kept at room temperature for 1 week, then made basic with 28% ammonia, and extracted with chloroform. The extract was washed with water, dried ($Na_2SO_4$), and evaporated to give a reddish syrup (200 mg), which was chromatographed on silica gel (6 g). Elution with chloroform–methanol (99 : 1) afforded (±)-reframidine (3) (105 mg) as a pale yellow syrup, spectral data of which were identical with those of an authentic sample [7] donated by Professor S. F. Dyke.

(*b*) To a solution of the isoquinolinium iodide (7) (1·0 g) in methylene chloride (200 ml), an excess of ethereal diazomethane was added at 0°. Next day the solvent was evaporated off. A solution of the residue in 6N-hydrochloric acid was kept at room temperature for 1 week, made basic with 28% ammonia, and extracted with chloroform. The extract was washed with water, dried ($Na_2SO_4$), and evaporated to give a reddish syrup (600 mg), which was chromatographed on silica gel (30 g). Elution with chloroform–methanol (99 : 1) afforded (±)-reframidine (3) (200 mg) as a pale yellow syrup, τ($CDCl_3$) 7·55 (3H, s, N·$CH_3$) and 3·54, 3·42, 3·35, and 3·32 (4H, each s, ArH).

We thank Professor S. F. Dyke for spectral data of reframidine. We also thank Mrs. A. Satoh, Mrs. C. Koyanagi, Miss A. Ujiie, Mr. T. Ohuchi, Miss R. Kato, Miss C. Yoshida, and Miss F. Yoshinaka for spectral measurements and microanalyses.

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